Ataxia telangiectasia: a “disease model” to understand cerebellar control of vestibular reflexes

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Abstract

Experimental animal models suggest that modulation of the amplitude and direction of vestibular reflexes are important functions of the vestibulo-cerebellum and contribute to the control of gaze and balance. These critical vestibular functions have been infrequently quantified in human cerebellar disease. In 13 subjects with ataxia telangiectasia (A-T), a disease associated with profound cerebellar cortical degeneration, we found abnormalities of several key vestibular reflexes. The vestibulo-ocular reflex (VOR) was measured by eye-movement responses to changes in head rotation. The vestibulo-collic reflex (VCR) was assessed with cervical vestibular-evoked myogenic potentials (cVEMPs), in which auditory clicks lead to EMG activity of the sternocleidomastoid muscle. The VOR gain (eye velocity/head velocity) was increased in all subjects with A-T. An increase of the VCR, paralleling that of the VOR, was indirectly suggested by an increase in cVEMP amplitude.

In A-T subjects, alignment of the axis of eye rotation was not with that of head rotation. Subjects with A-T thus manifested VOR cross-coupling; abnormal eye movements directed along axes orthogonal to that of head rotation. Degeneration of the Purkinje neurons in the vestibulo-cerebellum probably underlies these deficits. This study offers insights into how the vestibulo-cerebellum functions in healthy humans. It may also be of value to the design of treatment trials as a surrogate biomarker of cerebellar function that does not require controlling for motivation or occult changes in motor strategy on the part of experimental subjects.
**Introduction**

Vestibular reflexes play a vital role in assuring clear vision during motion of the head and body. Individuals in whom these reflexes do not function properly experience diminished visual acuity with head motion and postural instability. Vestibular function must be exquisitely adaptable to the expected changes of growth, development, aging, as well as to unexpected perturbations from disease and trauma. Experimental evidence, largely from animal models, points to the role of the vestibulo-cerebellum in the long-term adaptive control of the VOR that assures the precise matching of eye position to the timing (phase), and inverse amplitude and direction of head motion (Ito, 1970; Robinson, 1976; Schultheis and Robinson, 1981; Walker and Zee, 2005; Walker and Zee, 1999; Lisberger et al., 1984). During locomotion the orientation of the head dynamically changes with respect to gravity. In order to stabilize gaze and thus facilitate clear vision the axis of eye rotation of the VOR must remain parallel to the axis of head rotation. Experimental studies in macaques have shown that, unlike both vestibular afferents (Fernandez et al., 1972; Goldberg and Fernandez, 1971) and some neurons within the vestibular and deep cerebellar nuclei (Angelaki et al., 2004; Shaikh et al., 2005b; Shaikh et al., 2005a), Purkinje and granule cells in the nodulus and ventral uvula encode vestibular signals in a space-fixed frame of reference (Yakusheva et al., 2007). Indeed, dynamic reorientation of the axis of the VOR in response to head motion is impaired in monkeys with lesions of the cerebellar nodulus (Angelaki and Hess, 1995; Sheliga et al., 1999).

The vestibulo-collic reflex (VCR), by stabilizing the head in space, further facilitates clear vision during locomotion. In contrast to the VOR, there is much less
information about the contribution of the cerebellum to the control of the VCR. The sacculus provides input to the VCR, as inferred from studies demonstrating the evocation of motor responses in the neck by auditory stimulation (termed cervical vestibular evoked myogenic potentials (cVEMPs) (Colebatch, et al., 1994; Sheykholeslami, et al., 2000). We hypothesized that lesions that diminish inhibition through vestibulo-cerebellar projections to the vestibular nucleus would increase the gain of the VCR. cVEMPs are a clinically feasible way to infer the function of the VCR and have been used to characterize both peripheral (labyrinthine) and central (mid to lower pontine) vestibular lesions (Welgampola and Colebatch, 2005). Therefore it might be expected that individuals with vestibulo-cerebellar cortical dysfunction would have an abnormal gain (amplitude) of the VCR as reflected by increased amplitude of the cVEMP.

To learn more about the contribution of the cerebellum to the control of vestibular reflexes in humans we examined a group of individuals with ataxiatelangiectasia (A-T), an autosomal recessive disorder caused by mutation of the ATM gene (Savitsky et al., 1995). Persons with A-T develop diffuse cerebellar cortical degeneration with relative preservation of deep cerebellar nuclei (Firat, et al., 2005; Tavani, et al., 2003; Sardanelli, et al., 1995; Farina, et al., 1994; Crawford et al 1998). Progressive oculomotor dysfunction is prominent in A-T (Shaikh et al., 2009; Stell et al., 1989; Lewis et al., 1999; Baloh et al., 1978; Savitsky et al., 1995) but little is known about specific vestibular abnormalities. We hypothesized that the long-term adaptive control of amplitude, phase, and direction of vestibular reflexes that are mediated by the vestibular and deep cerebellar nuclei – the main target of inhibitory GABAergic
vestibulo-cerebellar Purkinje cell projections – would be impaired in individuals with advanced neurologic manifestations of A-T.
We studied in total 13 subjects with A-T and 11 healthy controls. The experimental protocols were approved by ethics committees at Zürich University Hospital and The Johns Hopkins University. Subjects gave informed consent before the experiment.

**Patient characteristics**

All experimental subjects met criteria for the diagnosis of A-T (Cabana et al., 1998), with abnormal chromosomal breakage following ionizing radiation, increased levels of serum alpha fetoprotein, and typical clinical and laboratory features of A-T (McConville et al., 1996; Stankovic et al., 1998; Sutton et al., 2004). Five subjects with A-T were studied specifically for three-axis vestibular testing in Zurich. The VOR testing of eight patients of the Johns Hopkins cohort comprises part of the baseline testing for a treatment trial (ClinicalTrials.gov ID NCT00640003). The individuals evaluated in Zurich were generally older (median 26 years, range 23 to 52) and express a slower rate of degeneration but are similarly impaired to the younger more typical subjects with A-T who were evaluated at Johns Hopkins (median 19 years, range 12 – 28). This difference is explained by inherent biases of subject volunteer recruitment through the A-T Society in the United Kingdom. The five Zurich subjects included four with homozygous or heterozygous “leaky” splice-site mutations of the ATM gene (Sutton et al., 2004; McConville et al., 1996) that are associated with a slower rate of degeneration but overall similar phenotype. All subjects with A-T had typical signs that are found with vestibulo-cerebellar lesions (table 1).
**Vestibular stimuli and eye movement recordings**

The five Zurich subjects were studied in a completely dark room in a three-dimensional vestibular turn table (Acutronic, Jona, Switzerland) that delivered three types of vestibular stimuli:

1) **Yaw rotations**: Earth vertical-axis rotations when the patient was oriented upright (see head caricatures in Figure 1A,D).

2) **Supine rotations**: Earth vertical-axis rotations when the patient was oriented supine (Figure 1B,E).

3) **Left ear down (LED) rotations**: Earth vertical-axis rotations when the patient was oriented on the left side (left ear down (LED) rotations, Figure 1C,F).

The rotations were in a clockwise or counter-clockwise direction about the earth-vertical axis, centered in the head, at a constant velocity of 100º/second (acceleration and deceleration 90º/second²). Rotations lasted one minute and were followed by a one minute post-rotational phase. 3D eye positions were simultaneously recorded. In these subjects eye movements were recorded with sclera search coils placed immediately around the limbus (Bergamin et al., 2001). The raw search coil signals were digitally sampled at 1,000 Hz and converted to eye position signals using interactive programs written in Matlab® (Mathworks; Natick, MA).

At Johns Hopkins, eight subjects were studied in a vestibular chair (Neurokinetics, Pittsburgh, PA) that delivered constant-velocity (clockwise or counter-clockwise, 60º/second) vertical-axis yaw rotations, each lasting one minute followed by a post-rotational phase of one minute. Horizontal and vertical eye positions were
simultaneously recorded using video oculography (VOG). Eye position was sampled at 60 Hz with monocular VOG (SMI® system). The data was saved for offline analysis.

There was no significant difference in VOR gain and time constant measured in the two experimental setups (t-test; p > 0.1), therefore, the results were combined for further analysis. In all subjects, horizontal VOR was measured during three horizontal rotation trials in each of the two directions. Thus 66 trials were used to compute horizontal VOR gain in healthy subjects and 76 trials in subjects with A-T. For the Zurich studies of torsion and vertical VOR gain, two rotation trials in each direction, a total of four rotation trials per subject, were used for further analysis. Thus 44 rotation trials were used in healthy subjects, and 52 in A-T.

**Eye movement data analysis**

The eye position data was further processed with interactive programs written in Matlab® (Mathworks; Natick, MA). Nystagmus cycles were interactively identified from the eye position signal. Eye position was differentiated to derive eye velocity with a Savitzky-Golay filter (Matlab, Mathworks, Natick, MA) of signal processing noise. We then derived the median value of the eye velocity during the slow phase of the given nystagmus (Straumann, 1991). The maximum VOR was calculated from the highest value two seconds after the onset of motion (prior to this time slow phases are generally not detected with the eye remaining at the orbital limit) and decay time constant computed from the successive slow phases following the onset of velocity decline. The slow-phase eye velocity data was first smoothed with a Savitzky-Golay filter (Matlab®, Mathworks; Natick, MA). The data was then fitted to an exponential using the function in equation (1)
\[ y(t) = A \times \exp(-t/\tau) + B \] \hspace{1cm} \ldots \ldots (1)

Here \( A \) is amplitude, \( \tau \) is the time constant of exponential decay and \( B \) is the baseline offset. The values of \( A, B, \) and \( \tau \) that best fit the data were estimated with a Matlab least-squares fitting algorithm (Matlab\textsuperscript{®}, Mathworks, Optimization Toolbox).

Although the data acquisition systems at the two institutes were different, there was no difference in the gain and time constant amongst the groups of healthy subjects recruited at these centers (Gain: One-way ANOVA, \( p = 0.21 \); Time constant: One-way ANOVA, \( p = 0.19 \)). We noticed minimal test-retest variability between data recorded during two independent trials in a given subject (correlation coefficient = 0.8; slope of the line fitted through scatter = 0.8). In our subjects we did not notice significant differences between the VOR gains during rightward versus leftward yaw rotation \( (p = 0.2) \); rostral versus caudal LED rotations \( (p = 0.37) \) or clock-wise versus counter-clockwise supine rotations \( (p = 0.36) \). Therefore, we lumped the data from two opposite directions for further analysis.

Equation (2) was used to compute the difference between the angular orientation of the head velocity and eye velocity vectors.

\[ \cos(\theta) = \frac{(i_e \times i_h + j_e \times j_h + k_e \times k_h)}{[((i_e + j_e + k_e)^{1/2}) \times ((i_h + j_h + k_h)^{1/2})]} \] \hspace{1cm} \ldots \ldots (2)

Here, \( (i_e, j_e, k_e) \) is a three-dimensional eye velocity vector, \( (i_h, j_h, k_h) \) is a three-dimensional head velocity vector, and \( \theta \) is the difference between the angular orientation of these two vectors.

The Matlab statistics tool box was used to perform statistical analysis; the difference between the two populations was considered significant when the \( p \) value was less than 0.05.
Auditory click-evoked cervical vestibular myogenic potentials (cVEMP)

The ten subjects evaluated for cVEMP each had normal hearing by bedside testing. cVEMP responses were recorded over the sternocleidomastoid muscle using a previously described procedure (Welgampola et al., 2008). A pair of headphones (Telephonics Corp., New York, NY) delivered unilateral rarefaction clicks. Clicks were 0.1 millisecond in duration, presented at a rate of 10 Hz, with a loudness at 60 to 103 dB NHL (NHL = normal hearing level, SPL = sound pressure level; 0 dB NHL = 45 dB SPL). Responses were analyzed for 80 milliseconds after the click. The signal was band-pass filtered from 20 Hz to 2 kHz. 128 sweeps were averaged and the responses were reproduced in a second set. The cVEMP amplitude was corrected for the underlying activity of the rectified EMG in the 10 msec prior to the onset of the stimulus using equation (3)

\[
\frac{(p13-n23)}{\text{mean rectified EMG potential}} \quad \ldots \ldots \ldots (3)
\]

Here p13 is the amplitude of the positivity and n23 is the negativity in the neck EMG during cVEMP.

The asymmetry ratio of the cVEMP responses was computed with equation (4).

\[
\text{Asymmetry ratio} = \% \left( \frac{\text{Left}-\text{Right}}{\text{Left}+\text{Right}} \right) \text{ corrected amplitude} \quad \ldots \ldots (4)
\]
Results:

**Vestibulo-ocular reflex (VOR)**

**VOR gain and time constant**

Representative examples of the slow-phase eye velocities of the per-rotational nystagmus during passive whole-body rotations in one healthy subject and one subject with A-T are illustrated in Figure 1. In the healthy subject, rotational nystagmus was predominantly in the plane of rotation (Figure 1A-C). The peak slow-phase velocity of the horizontal rotational nystagmus evoked during yaw rotation in this example was 58º/second with the turntable rotating at 100º/second (gain=0.58; time constant=11.2 sec; Figure 1A). Figure 1B illustrates an example of supine rotations in the same subject; peak slow-phase velocity of the torsional rotational nystagmus was 31º/second (gain=0.31; time constant=6.1 sec; Figure 1B). The peak slow-phase velocity of the vertical nystagmus evoked by left ear down (LED) rotation, was 40º/second (gain=0.4; time constant=7.9 sec; Figure 1C).

Figure 1D-F depict examples of horizontal, torsional and vertical slow-phase velocity during yaw, supine, and LED rotations in an A-T subject. The peak horizontal slow-phase velocity during yaw rotation was 98º/second (gain = 0.98 time constant=12.6 sec; Figure 1D). During supine rotations the peak torsional slow-phase velocity was 54º/second (gain = 0.54; time constant=7.3 sec; Figure 1E). Similarly, the peak slow-phase velocity of the vertical nystagmus evoked by LED rotations was 56º/second (gain = 0.56; time constant=5.8 sec; Figure 1F). Thus, in this A-T subject, the VOR gains were increased during rotation about each of the three axes. Data from 13 A-T and 11 healthy subjects are summarized in Figure 2 and Table 2. Each box and
whisker plot represents maximum VOR gain in a given group during one experimental paradigm. The horizontal line in the center of the notch represents the median, the notches represent the 95% confidence interval around median, the lengths of the boxes represent the 25th and 75th quartiles, and the whiskers represent the range. If the notches of the corresponding box and whisker plots do not overlap, the difference between the median is statistically significant (One-way ANOVA p < 0.05). The increase in the VOR gains in the subjects with A-T were statistically significant (One-way ANOVA, p<0.01), however, the VOR time constants were not significantly different from healthy subjects (One-way ANOVA, p>0.05).

**Directional abnormalities in VOR**

We measured two parameters to assess how well the eye velocity axis aligns with that of the head. First we compared the gains of main-axis and cross-axes components of the VOR. For instance, during yaw rotations in the healthy subject the horizontal eye component gain was 0.56; while the cross-axis, torsional and vertical component gains were 0.10 and 0.06 respectively. The same pattern was observed in all healthy subjects, as illustrated in Table 2. In contrast, in a representative example of a subject with A-T during yaw rotation, the horizontal eye component gain was 0.91; while enhanced, cross-axis, torsional and vertical component gains were 0.61 and 0.18, respectively. This finding was found in all A-T subjects (Table 2) and the difference between A-T and normal statistically significant (One-way ANOVA, p<0.01).

In healthy subjects, during supine and LED rotations the main-axis components of the VOR gains were 0.31 and 0.40 respectively. In contrast, the VOR gains of the cross axis components during these conditions were 0.10, 0.09 (horizontal and vertical
components, respectively, during supine rotations), and 0.11, and 0.15 (horizontal and
torsional components, respectively, during LED rotations). All healthy subjects showed
this pattern (Table 2). Although the overall VOR gains were increased in subjects with
A-T, this relationship of VOR cross coupling error was similar to that seen in the healthy
controls. The cross-axis VOR during LED and supine rotation was relatively less than
that measured during yaw axis rotation (Table 2).

We then compared the angular orientation of the VOR axes during each slow
phase of post- or per-rotational nystagmus with the angular orientation of the
corresponding head rotation axis. Figure 3 summarizes the differences in the
orientation of the VOR axis and that of head rotation during the three rotational
conditions. The difference in the orientation of the VOR axis and head rotation axis was
plotted along the y-axis, while each box-whisker plot illustrates one condition in a given
group of subjects. In healthy subjects, the axes of VOR deviated from the axes of head
rotation by 19.6 ± 7.7°. This is a significantly smaller deviation compared to A-T subjects
(57.8 ± 13.2°; one-way ANOVA, p<0.001). During supine rotations in healthy subjects
the axis of VOR was oriented 47.1 ± 15.9° away from the axis of head rotation. This is
significantly smaller compared to that found in subjects with A-T (67.6 ± 9.9°; one-way
ANOVA, p<0.001). In healthy subjects, the orientation of the axes of the VOR in yaw is
significantly less than that in LED and supine head rotation (one-way ANOVA, p <
0.001). This difference between axes is larger, but similar in subjects with A-T (one-way
ANOVA, p<0.001). During LED rotations, there was a similar increase in the mean
difference between the orientation of the VOR axis and head rotation axis in A-T (50.6 ±
14.3°) and healthy subjects (49.9 ± 19.9°). Both of these were significantly larger
compared to yaw rotations in healthy subjects (one-way ANOVA, p < 0.001), however, there was no significant difference between the deviation in the axis of VOR between A-T and healthy subjects.

**Vestibulocollic reflex: cervical vestibular evoked myogenic potentials (cVEMP)**

The cVEMP responses were measured in 10 of the 13 subjects with A-T. Two of these 10 subjects with A-T studied had absent responses (as is sometimes the case in normal subjects). Hence, further data analysis of cVEMP responses was performed in eight subjects with A-T. Figure 4 illustrates an example of click-induced, cVEMP in one subject with A-T. The response began with a positive (p13) peak at 11.6 ms, and subsequent negative peak at 16.8 ms (n23). Correction of cVEMP amplitude at 100 dB NHL amplitude in this example was 2.6. Mean corrected amplitude from the 16 ears (eight subjects with A-T) at 100 dB NHL sound level was 2.9 ± 1.2, a value significantly larger than that of controls, 1.2 ± 0.4 (one-way ANOVA, p<0.01), measured using the same technique (Figure 4E). All other measures of cVEMP were normal, including p13 initial latency (11.5 ± 0.7 ms on the right, left 12 ± 0.9 ms) n23 initial latency (18.5 ± 1.5 ms on the right, left 18.6 ± 1.8 ms), p13 peak latency (10.1 – 15.9 ms) and n23 peak latency (16.1 – 27.9 ms), asymmetry ratios (0.5 to 30%), and thresholds (79.7 ± 5.6 dB NHL)(Figure 4F). Increased corrected amplitude but a normal threshold of cVEMP argues against a peripheral cause for the increased cVEMP response (Welgampola, et al., 2008). The p13 and n23 amplitudes of the cVEMP responses lessened with the intensity of the auditory clicks (Figure 4B-D). The threshold for click-evoked cVEMP in
the given example was 85 dB NHL (normal range: 75 – 100 dB NHL).
Discussion

Impaired visual fixation during head motion and postural instability are common in cerebellar disease in general and especially prominent in subjects with A-T. All our subjects with A-T had strikingly abnormal vestibular function.

Increased VOR gain

A combination of diminished inhibitory input from GABAergic Purkinje projections causing disinhibition of the vestibular nuclei, and impaired cerebellar-dependent adaptation (Ito, 1970; Robinson, 1976; Lisberger, 1984), may account for an increase in VOR gain in individuals with cerebellar degeneration (e.g., Walker and Zee, 2005; 1999). This parallels the experience with most experimental lesions of the vestibulo-cerebellum in animals (Zee et al., 1981; Robinson, 1976). Our subjects with A-T consistently showed increased VOR gain, in concert with previous findings and our expectation.

Abnormal directional tuning of VOR

The cerebellum has an important role in directional tuning of the VOR. Lesions of the vestibulo-cerebellum in cats impair cross-axis adaptation of the VOR (Schultheis and Robinson, 1981) and individuals with cerebellar lesions show a directional abnormality in which there are inappropriately directed slow phases orthogonal to the axis of head rotation. This is known as VOR cross-coupling (Walker and Zee, 2005; 1999). Several pathophysiological mechanisms for VOR cross-coupling have been proposed. Lesions of the cerebellar nodulus and uvula in monkeys impair the orientation of eye velocity to the gravitational inertial axis (GIA) (Angelaki and Hess, 1995; Sheliga et al., 1999; Wearne et al., 1999). It is therefore reasonable to surmise that in humans too, the cerebellar nodulus and uvula have an important role in aligning
the axis of VOR to the axis of head rotation. The loss of cerebellar-mediated
adjustment to the relative synaptic strength of the converging canal inputs in the
vestibular nucleus (mathematically described as a 3x3 gain matrix) (e.g., Robinson,
1982) that normally compensates for anatomical misalignments between the
semicircular canals and the pulling directions of the orbital muscles might also cause
abnormal VOR cross-coupling (Walker and Zee, 2005). Minimal VOR cross-coupling
was noticed in healthy subjects during yaw rotations, and interestingly increase in
amount during supine and LED paradigms. We speculate that optimal calibrated output
of vestibular velocity storage, during the given plane of rotation, has a critical role in
attenuating nascent cross-coupled VOR responses. Studies show that human velocity
storage during on-axis LED and supine rotations is weaker in comparison to on-axis
yaw rotations (Tweed et al., 1994). Inaccuracy in the alignment of the axis of VOR with
the axis of head rotation during LED and supine rotations in our healthy subjects
supports our speculation that the output of velocity storage has a role in determining the
axis of compensatory eye rotation evoked by pure semicircular canal stimulation. It is
further speculated that in individuals with A-T mis-calibrated output of the velocity-
storage mechanism contributes to the VOR cross-coupling, even during yaw rotations.

An upward slow-phase of the cross-coupled response during yaw rotations is a
consistent observation in individuals with A-T, including those in our experimental
cohort. All but one of these subjects also had downbeat nystagmus with upward slow
phases. The slow-phase velocity of the spontaneous downbeat nystagmus was
considerably lower (Shaikh et al., 2009) than the peak slow-phase velocity of the
upwards drifts during yaw rotations, however. It is thus unlikely that upward eye velocity
during yaw rotation is simply a superposition of the spontaneous downbeat nystagmus.

**VOR time constant**

Velocity storage increases the frequency bandwidth of the VOR. In this way the
VOR can more faithfully compensate for the rapid decay of vestibular coding of
prolonged low-frequency rotation (Raphan, et al., 1979). Abnormally increased velocity
storage, as measured by a prolonged VOR time constant, was found following
experimental ablation in monkeys of the cerebellar nodulus and ventral uvula with some
extension of the lesion into the paravermis (Waespe et al., 1985). Thus, velocity
storage is under negative feedback regulation from the Purkinje neurons of nodulus and
ventral uvula. In extreme cases oscillations within the velocity storage mechanism,
known as periodic alternating nystagmus, emerge from this loss of inhibition from the
cerebellum. Although we saw periodic alternating nystagmus in eight experimental
subjects, we did not note a corresponding increase in the VOR time constant. In
individuals with cerebellar lesions the VOR time constant may or may not be increased,
presumably depending upon the extent of the lesion (Hain et al., 1988). As compared
to the horizontal VOR (during yaw rotations), the decay time constant of the vertical and
torsional components of the VOR (during LED and supine rotations, respectively) was
smaller. Relatively weak velocity storage in the neural pathways for the vertical and
torsional VOR in humans (Tweed et al., 1994) may explain these results.

**Increased VCR gain**

The VCR is a compensatory response of the neck muscles that helps to stabilize
the position of the head in space with movement of the body. The short bi- and tri-
synaptic pathways between vestibular end-organs and neck muscles indicates a rapid
pathway with minimal opportunity for external influence of the connection between the
two. (Suzuki et al., 1964; Uchino et al., 1997). Nonetheless, the cerebellum may
influence this pathway. For example, in decerebrate cats, sinusoidal yaw rotations
show a 90° phase lag between the 2nd order vestibular neuron and the neck motor unit
(Wilson et al., 1979; Ezure and Sasaki, 1978). Analogous to the VOR, the amplitude of
the VCR – as inferred from the amplitude of the sound-induced, sacculus-mediated
cVEMP – may be increased with lesions of the vestibular cerebellum. This could be
from a direct loss of inhibition upon central vestibulospinal pathways (as is presumably
the case for the VOR) or a disturbance in cerebellar adaptive mechanisms that control
the amplitude of the VCR as they do for the VOR (Marti et al., 2002). Here we
emphasize that the high cVEMP amplitudes do not imply a peripheral vestibular
syndrome with hypersensitivity to noise such as semicircular canal dehiscence. In our
subjects with A-T the auditory thresholds and latencies for eliciting a cVEMP response
were normal. Rather the increased VCR response likely reflects disinhibition and the
lack of a normal cerebellar adaptive mechanism upon sacculo-collic reflexes secondary
to Purkinje neuron degeneration.

There is other, less direct, evidence of a role for the cerebellum in the control of
sacculo-ocular reflexes. Lesions of the nodulus and ventral uvula lead to abnormalities
of the vertical translational vestibulo-ocular reflex that is presumably mediated by
stimulation of the sacculus. Spontaneous vertical nystagmus is also a feature of lesions
in the nodulus and ventral uvula; its source could be a bias within otolith-ocular
pathways (Walker et al., 2008b). Other means have recently been discovered by which
the cerebellum influences translational vestibulo ocular reflexes. Individuals with profound diffuse cerebellar degenerations show little compensatory eye movement response to interaural translations while monkeys with lesions in the nodulus/ventral uvula show a specific defect in transforming afferent inputs conveying head acceleration information into the correct eye velocity commands (Walker, et al., 2010). This type of abnormality implies an impaired neural integration in the interaural translational vestibuloocular reflex (Walker et al., 2008a).

Caveats

Contemporary views of motor symptoms in A-T have emphasized the role of extracerebellar (basal ganglia) as well as cerebellar degeneration (Shaikh et al., 2009) in the absence of extrapyramidal pathology. But degeneration of extracerebellar vestibular pathways is unlikely to explain our findings because such changes would necessarily reduce the gain of the vestibular reflexes that we found consistently increased. Functional changes in the control of vestibular reflexes were attributed to degeneration of the vestibulocerebellum based on the presence of other clinical oculomotor signs that point to lesions in the vestibulo-cerebellum (Table 1). Correlation of abnormally increased vestibular responses to vestibulocerebellar volume changes with high-resolution posterior fossae MRI might be possible, though confounded by difficulties in scanning subjects with A-T who frequently also manifest abnormal involuntary movements at rest.

Clinical implications and conclusions

Our findings have broad implications. Abnormal otolith-mediated reflexes with vestibulo-cerebellar lesions may contribute to the striking and characteristic pattern of
postural instability (omnidirectional sway) and difficulties with ambulation that individuals with lesions in this region experience (Diener et al., 1984). Furthermore, directional abnormalities and inability to reorient the axis of VOR has only been reported in monkeys with selective lesions of the nodulus and ventral uvula. These results suggest that testing the spatial orientation of the VOR under different orientations of the head with respect to gravity can be a marker of vestibulo-cerebellar disorders affecting the nodulus and ventral uvula in humans. Our results also suggest that cVEMPs may be used in the diagnosis of vestibulo-cerebellar disorders that lead to disinhibition of central VCR pathways. These new findings not only enhance our understanding of vestibular function in A-T, but also relate to contemporary views of the ways in which the cerebellum controls vestibular reflexes in healthy humans.

A key problem in translational research into potential therapies is identification of a reliable and meaningful outcome measure. The design of clinical studies in cerebellar disorders is particularly difficult, given substantial variation in motor performance with illness, fatigue, motivation, and occult changes in motor strategy to perform a task. Most trials require use of functional rating scales validated to specific disorders, and thus potentially assess a mixture of different impairments. Instrumented assessment of vestibular function is highly specific to pathophysiology, and could be a surrogate measure of cerebellar function presumably less confounded by these other factors.

**Figure/table legends**

Figure 1. Example of rotational VOR in a healthy control and A-T subject. Slow-phase eye velocities of the per-rotational nystagmus are plotted versus time. Each symbol
representing the eye velocity is the median value of the velocity computed from one
slow phase, and it is plotted at the median value of the time span during which the slow
phase was present (i.e. if a given slow phase of 0.4 seconds duration occurred between
time 2.1 and 2.5 seconds, the median eye velocity during that slow phase would be
plotted at 2.3 second mark on the x-axis). Black symbols represent mean slow phase
horizontal, red torsional, and cyan vertical (relative to the head), eye velocity. Arrows
mark the onset of rotations. (A,D) Example of yaw, (B,E) supine, and (C,F) LED
rotations. The caricatures in the inset of each panel represent the orientation of the
subject and dotted the grey line the axis of rotation.

Figure 2. (A) The comparison of VOR gain of A-T (solid box and whisker plots) to
healthy control subjects (dotted box and whisker plots) during all three planes of
rotation. (B) Comparison of the VOR time constant between A-T subjects and healthy
subjects.

Figure 3  Summary of differences in the angular orientation of the axis of eye velocity
and of head velocity. The difference in the orientation of the VOR axis and head
rotation axis was plotted along the y-axis, while each box-whisker plot illustrates one
condition in a given group of 13 subjects with A-T and the 11 normal subjects.

Figure 4  An example of averaged unrectified EMG in the ipsilateral sternocleidomastoid
(SCM) muscle evoked by 0.1 ms 100 dB (A), 90 dB (B), 85 dB (C), and 80 dB (D)
normal hearing level click stimuli to the right ear. The raw electrical activity is plotted
along the y-axis while the time is on the x-axis. The threshold for cVEMP responses in
this example, 80 dB normal hearing level, was within normal range. (E) Summary of
corrected amplitude from eight A-T subjects (black box-whisker plots) and 45 age-
matched control subjects (grey box-whisker plots). (F) The summary of threshold values in subjects with A-T. The click intensity (dB normal hearing level) is plotted on the x-axis and the corresponding corrected amplitudes are plotted on the y-axis. Grey zone represents the normal values of threshold intensity in age-matched healthy subjects.

Table 1. Summary of clinical oculomotor signs in experimental subjects with A-T. Table 2. The table illustrates a summary of VOR gain from 11 healthy and 13 A-T subjects. Mean VOR gain during each three types of rotation trials are sorted in columns; while the rows depict the VOR gain sorted by the plane of eye rotation. Values in bold characters represent the mean VOR gain for eye rotations along the axis parallel to that of head rotation (i.e., horizontal VOR gain during yaw rotations; vertical VOR gain during on-axis LED rotations; and torsional VOR gain during supine rotations; corresponding median values are illustrated in Figure 2A). The values of mean VOR gain along axes orthogonal to that of head rotations are illustrated in italics.

Table 3. The summary of the decay time constants of the VOR responses.
Table 1

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Clinically observed oculomotor signs</th>
<th>Anatomical localization of the lesion based on clinically observed oculomotor sign</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAN</td>
<td>Horizontal gaze-evoked nystagmus at primary gaze</td>
</tr>
<tr>
<td>P 1</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>P 3</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>P 4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>P 5</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>P 6</td>
<td>Yes</td>
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<td>P 7</td>
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<tr>
<td>P 12</td>
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<td>Yes</td>
</tr>
<tr>
<td>P 13</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 2

<table>
<thead>
<tr>
<th>VOR gain in healthy subjects (mean ± standard deviation)</th>
<th>Head Horizontal</th>
<th>Head Vertical</th>
<th>Head Torsion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Horizontal</td>
<td>0.55 ± 0.20</td>
<td>0.20 ± 0.20</td>
<td>0.22 ± 0.15</td>
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<tr>
<td>Eye Vertical</td>
<td>0.15 ± 0.12</td>
<td>0.43 ± 0.14</td>
<td>0.21 ± 0.15</td>
</tr>
<tr>
<td>Eye Torsion</td>
<td>0.11 ± 0.06</td>
<td>0.11 ± 0.09</td>
<td>0.34 ± 0.16</td>
</tr>
</tbody>
</table>

VOR gain in A-T subjects (mean ± standard deviation)

<table>
<thead>
<tr>
<th>Head Horizontal</th>
<th>Head Vertical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Horizontal</td>
<td>0.91 ± 0.34</td>
</tr>
<tr>
<td>Eye Vertical</td>
<td>0.45 ± 0.19</td>
</tr>
<tr>
<td>Eye Torsion</td>
<td>0.21 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>Head Horizontal</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Eye Horizontal</strong></td>
<td>12.0 ± 4.8</td>
</tr>
<tr>
<td><strong>Eye Vertical</strong></td>
<td>6.7 ± 2.9</td>
</tr>
<tr>
<td><strong>Eye Torsion</strong></td>
<td>8.6 ± 3.2</td>
</tr>
</tbody>
</table>

**Table 3**

VOR time constant in healthy subjects (mean ± standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>Head Horizontal</th>
<th>Head Vertical</th>
<th>Head Torsion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Horizontal</strong></td>
<td>11.7 ± 5.5</td>
<td>13.6 ± 8.7</td>
<td>14.6 ± 9.9</td>
</tr>
<tr>
<td><strong>Eye Vertical</strong></td>
<td>14.2 ± 6.89</td>
<td>6.3 ± 1.67</td>
<td>10.9 ± 10.0</td>
</tr>
<tr>
<td><strong>Eye Torsion</strong></td>
<td>8.1 ± 3.0</td>
<td>8.6 ± 5.0</td>
<td>8.7 ± 6.3</td>
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</table>
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